

## **Cardiovascular disease, cancer and mortality among people with type 2 diabetes and alcoholic or non-alcoholic fatty liver disease hospital admission**

Running title: liver disease outcomes in type 2 diabetes

Sarah H Wild PhD<sup>1</sup>, Jeremy J. Walker PhD<sup>1</sup>, Joanne R Morling PhD<sup>2</sup>, David A McAllister MD<sup>1</sup>, Helen Colhoun MD<sup>3</sup>, Bassam Farran PhD<sup>3</sup>, Stuart McGurnaghan<sup>3</sup>, Rory McCrimmon MD<sup>4</sup>, Stephanie H Read PhD<sup>1</sup>, Naveed Sattar PhD<sup>5</sup>, Christopher D Byrne PhD<sup>6,7</sup> on behalf of the Scottish Diabetes Research Network Epidemiology Group

<sup>1</sup> Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, UK

<sup>2</sup> Division of Epidemiology and Public Health, University of Nottingham, UK

<sup>3</sup> Institute of Genetics and Molecular Medicine, University of Edinburgh, UK

<sup>4</sup> Division of Molecular & Clinical Medicine, University of Dundee, UK

<sup>5</sup> Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK

<sup>6</sup> Nutrition and Metabolism, Faculty of Medicine, University of Southampton, UK

<sup>7</sup> NIHR Southampton Biomedical Research Centre, University Hospital Southampton, UK

### **Corresponding author:**

Professor Sarah Wild, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, UK.

[Sarah.wild@ed.ac.uk](mailto:Sarah.wild@ed.ac.uk). Tel: +44 131 651 1630 Fax: +44 131 650 6868

**Word count:** 3,805

**Number of tables and figures:** Four tables in main text (one table and three figures in supplementary material).

## **Abstract**

**OBJECTIVE** To describe associations between alcoholic fatty liver disease (ALD) or non-alcoholic fatty liver disease (NAFLD) hospital admission and cardiovascular disease (CVD), cancer, and mortality in people with T2DM.

**RESEARCH DESIGN AND METHODS** We performed a retrospective cohort study using linked population-based routine data from the diabetes register, hospital, cancer and death records for people aged 40-89 years, diagnosed with T2DM in Scotland 2004-2013 who had one or more hospital admission records. Liver disease and outcomes were identified using International Classification of Diseases codes. We estimated hazard ratios from Cox proportional hazards models, adjusted for key risk factors (aHRs).

**RESULTS** There were 134,368 people with T2DM (1707 with ALD and 1452 with NAFLD) with mean follow-up of 4.3 years for CVD and 4.7 years for mortality. Among people with ALD, NAFLD or without liver disease hospital records respectively there were: 378, 320 and 21,873 CVD events, 268, 176 and 15,101 cancers and 724, 221 and 16,203 deaths. For ALD and NAFLD respectively, aHRs (95% CIs) compared to the group with no record of liver disease were: 1.59 (1.43, 1.76) and 1.70 (1.52, 1.90), for CVD; 40.3 (28.8, 56.5) and 19.12(11.71 31.2), for hepatocellular cancer (HCC); 1.28 (1.12, 1.47) and 1.10 (0.94, 1.29) for non-HCC cancer; 4.86 (4.50, 5.24) and 1.60 (1.40, 1.83) for all-cause mortality.

**CONCLUSIONS** Hospital records of ALD or NAFLD are associated, to varying degrees, with increased risk of CVD, cancer and mortality in people with T2DM.

Abstract Word Count: 239

Alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM) are common diseases and ALD or NAFLD often co-exist with T2DM. There is evidence of a bi-directional relationship between liver disease and T2DM. Both ALD and NAFLD appear to be risk factors for T2DM, and T2DM is a risk factor for more severe liver disease in people with ALD or NAFLD (1-6). The increased risk of CVD, cancer and mortality among people with type 2 diabetes, compared to people without diabetes, is well known (7-9). There is evidence of an association between NAFLD and CVD among people with and without diabetes although it is recognised that further information is needed in terms of describing the natural history of NAFLD with regard to both its hepatic and extra-hepatic complications(10; 11), On the basis of existing evidence it appears that more advanced liver disease is associated with higher risk of complications (11; 12). Fewer data are available for the association between ALD and key health outcomes in people with T2DM. It is not clear how alcoholic or non-alcoholic etiology influences the risk of complications of liver disease(13) although there is a suggestion that fatty liver probably confers increased cardiovascular risk regardless of etiology and lipid phenotype(14).

In a Danish cohort with cirrhosis, of whom 10% had diabetes (and 25% had any co-morbidity), co-morbidity was associated with synergistic increases in mortality compared to a matched control population (15). Another Danish study compared incidence of several co-morbidities (including diabetes) identified from hospital records over a median of 2.6 years, in people with a hospital diagnosis of alcoholic cirrhosis, no record of viral hepatitis or of the outcomes of interest, with age and sex matched controls without cirrhosis (16). During follow-up, 738 people developed diabetes and the hazard ratio (95% CI) was 5.54 (4.94–6.21). The authors noted that

the extremely high mortality among people with ALD meant that few subjects lived long enough to develop co-morbidity and there was the potential for confounding by cigarette smoking. We have not identified any studies of the effect of ALD on mortality, CVD and cancer among people with T2D.

There is limited evidence for the association between NAFLD and mortality or CVD in people who have T2DM. A US cohort study of 337 people with T2DM, of whom 116 were diagnosed with NAFLD based on imaging or liver biopsy, suggested NAFLD was associated with increased all-cause mortality [age, sex and duration of diabetes adjusted hazard ratio 2.2; 95% confidence interval (CI) 1.1-4.2), mean follow-up 10.5 years] (17). An Italian study of 2103 people with T2DM of whom 157 had NAFLD, showed that NAFLD was associated with increased risk of incident CVD over 6.5 years: hazard ratio (95% CI) 1.9 (1.2-2.6) adjusted for age, sex, smoking, diabetes duration, LDL-cholesterol, medication and metabolic syndrome (18).

Currently, it is not possible to identify diagnoses of common liver diseases from routinely collected health data at a whole population level. However, ALD and NAFLD can be identified from hospital records in large population-based studies with record linkage to identify morbidity and mortality. The aim of our study was to describe event rates for CVD, cancer, and mortality among a type 2 diabetes cohort for people ALD, NAFLD and without records of liver disease. We also aimed to compare relative risks of CVD, cancer, all cause and cause-specific mortality for ALD and NAFLD compared to the group with no record of liver disease within the type 2 diabetes cohort.

## **Research Design and Methods**

### **Study population and survival time**

We conducted a retrospective cohort study using data from a 2014 extract of the Scottish Care Information-Diabetes (SCI-Diabetes) national population-based register (19) for people diagnosed with T2DM in Scotland between 1 January 2004 and 31 December 2013, who were aged 40-89 years during the study period and had a record of one or more hospital admissions. The Information Services Division (ISD) of NHS National Services Scotland (NHSNHS) linked the diabetes data to national mortality records, the cancer registry and hospital discharge records. Generation of the anonymised, linked data set was approved by the Scotland A multi-centre research ethics committee (reference 11-AL-0225), Caldicott guardians and the NHSNHS Privacy Application Committee (reference 33/11).

We excluded people with International Classification of Disease (ICD) codes for viral hepatitis, auto-immune hepatitis, hemochromatosis and any of cirrhosis, fibrosis, sclerosis or portal hypertension with no mention of ALD or NAFLD (see table 1 for ICD codes used to identify these conditions). Entry date to the cohort was date of diagnosis of diabetes. Exit date for CVD and cancer analyses was based on date of the first CVD event or cancer registration after diagnosis of diabetes or 31 December 2013 for people that neither died nor had a CVD or cancer event recorded by that date, with censoring at date of death where appropriate. Exit date for mortality analyses was date of death or 31 December 2013 for survivors to that date. Follow-up was censored at date of death from another cause for cause-specific mortality. Survival time for each analysis was from date of diagnosis of diabetes to censoring or date of exit.

## **Exposure and outcomes**

ALD and NAFLD were identified from the presence of the International Classification of Disease (ICD) codes listed in the relevant columns of Table 1 in any diagnosis field of a hospital admission record either before or after diagnosis of diabetes or in a death record. Individuals with records of both ALD and NAFLD (n=116) were classified as having ALD, because mention of ALD suggests that alcohol intake would have been higher at some point in the patient's history, than that allowed for a diagnosis of NAFLD.

CVD and date of event was identified from the presence of CVD codes as listed in Table 1 in any position on death and hospital records. Cancer events were identified from cancer registry and death records. Date of death was derived from national mortality records. Cause-specific mortality was defined using the codes listed in Table 1 in the primary cause-of-death field.

### **Statistical analysis**

People with missing data were excluded in order to perform a complete case analysis. We compared the characteristics of people with and without complete data. Cox regression models were fitted in which ALD or NAFLD were the exposures. Models were adjusted for age; sex; socio-economic status (SES, described further below); smoking status (current, former and never smoker categories); hypertension/anti-hypertensive treatment, defined below; high cholesterol/lipid lowering treatment, defined below; glycated haemoglobin (HbA1c) using measures closest to date of diagnosis of diabetes, and record of CVD history, prior to diagnosis of T2DM.

We used the Scottish Index of Multiple Deprivation (SIMD)

(<http://www.scotland.gov.uk/Resource/Doc/933/0115249.pdf> (accessed 22

September 2016) as the measure of SES. SIMD is a small-area-based ranked measure which combines 38 indicators of deprivation across seven domains. Rankings of the 6,505 geographical areas recorded in SIMD were included in models as quintiles (fifths) of the distribution where the first and fifth quintiles correspond to the most and least deprived groups in the population, respectively.

The binary marker of hypertension/anti-hypertensive treatment was derived from measured blood pressure ( $\geq 140$  mmHg systolic or  $\geq 90$  mmHg diastolic) or prescription history of anti-hypertensives (angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blocking agents, calcium channel blockers, or diuretics) using data recorded closest to diagnosis of diabetes. A similar approach was used to construct the high cholesterol/lipid-lowering treatment indicator, which combined measured values of serum cholesterol  $> 5$  mmol/l and prescription records for lipid-modifying medications.

There was little evidence of interaction between liver disease status and sex; and the two exceptions were marginally significant at the conventional 5% level: (i) for HCC mortality, the interaction of ALD with sex yielded  $p = 0.04$ ; (ii) for non-HCC cancer mortality, the interaction of NAFLD / NASH with sex returned  $p = 0.05$ . All other interaction terms yielded  $P > 0.1$ . We have therefore adjusted for sex instead of constructing sex-specific models.

In sensitivity analyses we excluded individuals with prevalent CVD or cancer at diagnosis of diabetes from a further Cox model as described above and omitted the prevalent CVD or cancer variables to describe the association between ALD or NAFLD and incident CVD or incident cancer after diagnosis of diabetes.

All Cox models were fitted using the PHREG procedure in SAS software (Version 9.4). Difference in direct adjusted survival curves between those with and without



ALD or NAFLD were obtained using SAS routines published by Wang & Zhang (20) and are presented graphically.

## **Results**

We identified a cohort of 134,368 people who were aged 40-89 years and diagnosed with T2DM during the study period who had a record of at least one hospital admission and no record of any of viral hepatitis, auto-immune hepatitis, haemochromatosis or liver disease of unspecified cause and who had complete data for SES, smoking status, hypertension/treatment status, high cholesterol/treatment status and HbA1c (see figure 1 in online supplemental material for a flow chart describing the cohort selection). Distribution of characteristics of people who were excluded due to missing data were similar to those of people without liver disease in the study cohort. Mean age at diabetes diagnosis was 62.7 years in both groups; the proportion of men was 54.0% in those with missing data against 54.9% in people with no liver disease; and the corresponding respective proportions with prevalent CVD were 19.2% and 19.1%.

The study cohort therefore included 134,368 people. Mean follow-up varied between 4.3 years for CVD outcomes and 4.7 years for mortality. There were 1,707 people (1.3%) with a record of ALD and 1,452 (1.1%) with a record of NAFLD of whom 8.9% and 19% respectively had a record of liver biopsy. For the ALD group, the mean age at the first ALD-related hospital admission was 57.4 years and mean age at DM diagnosis for this group was 59.3 years. For the NAFLD group, the mean age at the first hospital admission mentioning NAFLD was 58.3 years and mean age at DM diagnosis was 58.7 years. There were statistically significant differences in many characteristics by liver disease status, partly reflecting the large sample size even

when absolute differences were small and of questionable clinical relevance (see Table 2). Key differences between groups were that people with a history of hospital admission with ALD and NAFLD were younger than the group without liver disease and there was a larger proportion of men and smokers among the ALD group and a smaller proportion of men among the NAFLD group than among other groups. Mean body mass index was lowest among the ALD group and highest among the NAFLD group. The number of outcomes, duration of follow-up and crude event rates by liver disease status are shown in Table 3. The most common causes of death among the “other causes” groups, regardless of liver disease status, were respiratory diseases which accounted for about 18% of “other” deaths in the ALD group and 30% of “other” deaths in the NAFLD and no liver disease groups. Diseases of the digestive system (including liver disease) accounted for 18% of “other” deaths in the ALD group, 14% in the NAFLD group and 10% in the no liver disease groups. Other cardiovascular and endocrine diseases contributed 12% and 10%, 18% and 14% and 17% and 11% to the “other causes of death” groups for people with ALD, NAFLD and no liver disease respectively.

Table 4 shows adjusted hazard ratio estimates derived from Cox models for the associations between ALD or NAFLD and outcomes of interest. Lung cancer was the most common specific cancer among the ALD and no liver disease groups but colorectal cancer was the most common cancer among people with history of NAFLD. None of the associations between liver disease and individual common cancers was statistically significant.

The association with incident/recurrent CVD was similar for both types of liver disease. HRs for all-cause mortality were elevated for both liver disease groups and

were higher for the ALD group than the NAFLD group. The association with non-HCC cancer-related incidence was statistically significant for the ALD group.

The sensitivity analyses excluding people with prevalent CVD or cancer at diagnosis of diabetes resulted in similar associations to those for recurrent/incident CVD and cancer (see Table 1 in supplemental material).

The differences in direct adjusted survival between people with and without history of hospital admission with ALD or NAFLD derived from all-cause mortality are shown in Figures. 2 and 3 in the supplemental material respectively. Declines in survival relative to the no liver disease group over time were much steeper for the ALD group than for the NAFLD group.

## **Discussion**

Our novel data in a national cohort show that people with T2DM who have hospital records of either ALD or NAFLD are at increased risk of mortality from all-causes, CVD and HCC, as well as being at increased risk of incident/recurrent CVD events compared to people without records of liver disease. These findings extend those from previous studies of outcomes of cirrhosis in general populations (21-23) by including a wider definition of liver disease and non-fatal outcomes, separating the NAFLD group from the broader non-alcoholic cirrhosis group, by describing CVD incidence in both ALD and NAFLD groups and by limiting the study population to people with type 2 diabetes.

The largest study to date of a general population (the Third National Health and Nutrition Examination Survey, NHANES III), that is relevant to our NAFLD data, investigated the association between hepatic steatosis and NASH identified from

retrospective examination of ultrasound images originally performed to identify gallstones and liver enzyme concentrations measured in 1988-94 and mortality up to 2006 (24). Mortality from all causes, cardiovascular disease, cancer, or liver disease among people with steatosis or steatohepatitis was similar to that among participants without steatosis. It is likely that NHANES III participants had mild liver disease, as emphasised in the correspondence following publication of the paper (25). It is plausible that resolution of mild liver disease occurred among some NHANES III participants during follow up due to lifestyle change (26). Resolution of mild NAFLD over time would be expected to attenuate any association between liver disease at baseline and premature mortality. Other important differences are that our study was undertaken in an older population of people with type 2 diabetes in contrast to the population based sample and retrospective review of ultrasound images for NHANES III, among whom NAFLD was identified from hospital records.

A recent study reported heterogeneous associations between alcohol consumption and cardiovascular disease and found stronger associations between heavy alcohol intake and fatal cardiovascular disease (than non-fatal disease) that are consistent with our findings for the association between ALD and CVD mortality and incident/recurrent CVD (27).

Our findings showing an association between NAFLD and cardiovascular disease are consistent with a recent systematic review and meta-analysis of data from 16 prospective and retrospective studies that were not limited to people with diabetes (11). The meta-analysis included 34,043 people among whom 36% had NAFLD identified by imaging or biopsy and approximately 2,600 CVD outcomes occurred over a median of almost seven years of follow-up. The random effect summary

odds ratio for the association between NAFLD and CVD was 1.64, 95% CI 1.26–2.13 (11). Our point estimates for the association between NAFLD and both all-cause mortality and cardiovascular disease outcomes are similar to those of the small cohort studies described earlier (17) (18) but our estimates are more precise as would be expected given the larger study population.

A large Finnish study identified increased incidence of multiple types of cancer in addition to HCC among people with severe ALD and it is possible that our study lacked power to detect these associations (28). NAFLD has been associated with increased risk of colonic cancer (29), adenomatous polyps (30) and right sided colonic tumours (31). Further research is required to establish whether NAFLD is associated with other extra-hepatic cancers.

As for all studies using routine data there is potential for misclassification in our study. We identified NAFLD from hospital records in 1.1% of people with T2DM and at least one hospital admission record, a considerably smaller proportion than reported in population based studies of people with T2DM that have been able to characterise liver disease status more accurately (32)(33). The proportion we found is closer to the prevalence of clinically significant liver disease identified using liver ultrasound and non-invasive measures of NASH, hepatic fibrosis and systemic inflammation of 2.2% in participants in the Edinburgh Type 2 Diabetes Study (32). Markers of liver injury have only recently been included in the diabetes electronic health record and so were not available for use as an alternative marker of liver disease in this study.

In our study, we were not able to identify people with diagnoses of liver disease established solely in ambulatory care and such individuals are likely have less severe liver disease than people with a diagnosis in hospital admission records. The

absolute event rates that we report for the liver disease groups are therefore likely to be applicable to people with T2DM who have more advanced liver disease. With the exception of the associations between ALD and all-cause mortality and between both types of liver disease and HCC incidence or mortality the strength of the associations between liver disease and other outcomes was modest (HRs<1.70). However it is important to note that people with liver disease diagnosed solely in ambulatory care and with undiagnosed liver disease, who form a large sub-group of people with type 2 diabetes, are included in our comparison group. The absolute risks of the outcomes of interest in this sub-group of people who, in general, have less severe liver disease are expected to be intermediate between people without liver disease and people with severe liver disease who are likely to form the majority of our population of people with a record of hospital admission with liver disease (11,12). Consequently, we expect that the relative risks describing the association between severe liver disease and outcomes of interest would be larger than we have reported if we had been able to exclude people with liver disease from the comparison group. It will only be possible to estimate the size of this presumed bias when there are robust ways of identifying people with all levels of severity of liver disease and their risk of outcomes of interest at a population level. Our estimates of the strength of the association between NAFLD and mortality or CVD are consistent with those of other studies that included people with the whole spectrum of NAFLD and in which there are fewer concerns about ascertainment and misclassification bias (11,17,18). This suggests that the opposing effect of the different biases in the way we have identified the NAFLD and comparison groups are approximately balanced, but this hypothesis clearly requires testing when suitable data are available. It is possible that excluding people with missing data on covariates may

have influenced the strength of the associations that we observed but, as noted above, characteristics of people with missing data were similar to those of people without liver disease.

Although we have identified differing HRs for outcomes by liver disease status for all-cause mortality and cancer, it is interesting that the association between liver disease and increased risk of incident/recurrent CVD in our study was similar for both ALD and NAFLD. Despite the concerns about potential bias in our study noted above the association between NAFLD and incident/recurrent CVD that we describe was similar to that reported in a meta-analysis of studies that included people without diabetes and used other ways of identifying NAFLD (11). These findings suggest that liver disease per se may influence risk of CVD although it remains possible that common risk factors underlie risk of both liver disease and CVD.

We could not identify the date of diagnosis of liver disease and assumed that liver disease was present at diagnosis of diabetes. Mean age at diagnosis of diabetes and at hospital admission with first mention of liver disease was similar, suggesting that liver disease is likely to have been present before diagnosis of T2DM in many people. Our study included a relatively short median follow-up time because we only used data from 2004, the point from which the diabetes register in Scotland has been almost complete. Any time-varying effect of liver disease could only be investigated in a large well-characterised cohort of people that includes repeated assessment of liver disease and diabetes status.

The strengths of our study include the population-based nature of the national electronic record that captures data for >99% of people with a diagnosis of diabetes in Scotland and the availability of linkage to quality-assured hospital admission,

cancer registration and mortality data for the whole population (for more information, see <http://www.isdscotland.org/Products-and-Services/Data-Quality/Assessments/>).

We excluded people with no record of hospital admission from the comparator group to reduce bias arising from inclusion of a healthier sub-group of people with T2DM and people who had not had the opportunity to have liver disease or outcomes of interest ascertained by investigations performed during a hospital admission. We believe that, despite the limitations discussed above, the approach we have taken is the most appropriate approach to identify liver disease using routine health care data in population-based studies at present. It will be possible to describe longer-term outcomes of history of hospital admission with liver disease in future data linkages.

Our data from a national cohort of people with T2DM show for the first time that history of hospital admission with ALD or NAFLD is associated with increases in incident/recurrent CVD, cancer, all-cause and selected cause-specific mortality and independently of major risk factors. This measure of ALD or NAFLD is therefore associated with further increases risk of early mortality, CVD and cancer among people with T2DM beyond the risks associated with T2DM and key risk factors alone (7-9). The early stages of ALD and NAFLD are reversible following lifestyle changes such as reduction in alcohol consumption, weight loss and increases in physical activity. Our data suggest that clinicians should support their patients with T2DM and liver disease to make lifestyle changes where appropriate to reduce the increased risks of mortality and morbidity associated with more severe liver disease as well as improving glycemic control. Although there is some evidence of benefit of pioglitazone in patients with NAFLD (34), side effects of this agent have precluded its widespread use. Treatment with glucagon-like peptide 1 receptor agonists is



effective to treat hyperglycaemia for many patients with T2DM, and treatment with liraglutide has also shown recent promise in some patients with NASH (35).

However, since there are no licensed treatments for chronic liver disease and lifestyle change is notoriously difficult to achieve, further research is needed to identify effective treatments for both liver disease and its extra-hepatic complications among people with type 2 diabetes and to establish the role of differential follow-up among people with diabetes and liver disease.

**Acknowledgements.** This work was supported by funding from the Scottish Government through the Scottish Diabetes Group. Diabetes data for Scotland are available for analysis thanks to numerous healthcare staff who enter the data and people and organisations (people with diabetes, the Scottish Care Information – Diabetes Collaboration [SCI-DC] Steering Group, the Scottish Diabetes Group, the Scottish Diabetes Survey Group, the managed clinical network managers and staff in each Health Board) involved in providing data, setting up, maintaining and overseeing SCI-DC. The Scottish Diabetes Research Network is supported by National Health Service (NHS) Research Scotland, a partnership involving Scottish NHS Boards and the Chief Scientist Office of the Scottish Government. NS acknowledges European Federation of Pharmaceutical Industries Associations (EFPIA) Innovative Medicines Initiative Joint Undertaking (EMIF) grant number 115372 which partially supports his contribution to this paper. CDB is supported in part by the Southampton National Institute for Health Research Biomedical Research Centre.

**Funding.** Data linkage was funded by the Scottish Government through the Scottish Diabetes Group.

**Conflicts of Interest.** The authors have no conflicts of interest to declare.

**Author Contributions.** S.H.W and C.D.B performed the literature search. S.H.W., J.R.M, J.J.W and C.D.B designed the study and the analysis plan. Data were acquired as part of routine clinical care. H.C., S.M.C. and B.F. contributed to generation of the data. J.J.W. prepared and analysed the data and prepared the figures. J.J.W., S.H.W. and C.D.B. wrote the first draft of the manuscript. All authors contributed to data interpretation, critically reviewed the manuscript for important intellectual content and approved the final version. S.H.W. is the guarantor for the

work. The work was performed on behalf of the Scottish Diabetes Research Network Epidemiology Group. Findings of preliminary analyses relating to part of this work were presented at the Diabetes UK Annual Professional Conference in March 2017 and at the European Association for the Study of Diabetes in September 2017.

Further members of the Scottish Diabetes Research Network epidemiology group are Robert Lindsay, Graham Leese, John McKnight, John Petrie, Sam Philip.

## References

1. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH: Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol* 2000;32:209-217
2. Holstein A, Hinze S, Thiessen E, Plaschke A, Egberts EH: Clinical implications of hepatogenous diabetes in liver cirrhosis. *J Gastroenterol Hepatol* 2002;17:677-681
3. Hickman IJ, Macdonald GA: Impact of diabetes on the severity of liver disease. *Am J Med* 2007;120:829-834
4. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM: Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol* 2015;62:1148-1155
5. Byrne CD, Targher G: NAFLD: A multisystem disease. *J Hepatol* 2015;62:S47-S64
6. Raff EJ, Kakati D, Bloomer JR, Shoreibah M, Rasheed K, Singal AK: Diabetes Mellitus Predicts Occurrence of Cirrhosis and Hepatocellular Cancer in Alcoholic Liver and Non-alcoholic Fatty Liver Diseases. *J Clin Transl Hepatol* 2015;3:9-16
7. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjornsdottir S, Wedel H, Clements M, Dahlqvist S, Lind M: Excess Mortality among Persons with Type 2 Diabetes. *N Engl J Med* 2015;373:1720-1732
8. Walker JJ, Brewster DH, Colhoun HM, Fischbacher CM, Leese GP, Lindsay RS, McKnight JA, Philip S, Sattar N, Stockton DL, Wild SH: Type 2 diabetes, socioeconomic status and risk of cancer in Scotland 2001-2007. *Diabetologia* 2013;56:1712-1715
9. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J: Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215-2222
10. Targher G, Day CP, Bonora E: Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010;363:1341-1350
11. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C: Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. *J Hepatol* 2016;65:589-600
12. Lonardo A, Sookoian S, Pirola CJ, Targher G: Non-alcoholic fatty liver disease and risk of cardiovascular disease. *Metabolism* 2016;65:1136-1150
13. Volzke H: Multicausality in fatty liver disease: is there a rationale to distinguish between alcoholic and non-alcoholic origin? *World J Gastroenterol* 2012;18:3492-3501
14. Loria P, Marchesini G, Nascimbeni F, Ballestri S, Maurantonio M, Carubbi F, Ratzliff V, Lonardo A: Cardiovascular risk, lipidemic phenotype and steatosis. A comparative analysis of cirrhotic and non-cirrhotic liver disease due to varying etiology. *Atherosclerosis* 2014;232:99-109
15. Jepsen P, Vilstrup H, Andersen PK, Lash TL, Sorensen HT: Comorbidity and survival of Danish cirrhosis patients: a nationwide population-based cohort study. *Hepatology* 2008;48:214-220
16. Jepsen P, Lash TL, Vilstrup H: The clinical course of alcoholic cirrhosis: development of comorbid diseases. A Danish nationwide cohort study. *Liver Int* 2016;36:1696-1703

17. Adams LA, Harmsen S, St Sauver JL, Charatcharoenwitthaya P, Enders FB, Therneau T, Angulo P: Nonalcoholic fatty liver disease increases risk of death among patients with diabetes: a community-based cohort study. *Am J Gastroenterol* 2010;105:1567-1573
18. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C, Arcaro G: Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 2007;30:1212-1218
19. McKnight JA, Morris AD, Cline D, Peden N, Fischbacher C, Wild S: Implementing a national quality assurance system for diabetes care: the Scottish Diabetes Survey 2001-2006. *Diabet Med* 2008;25:743-746
20. Wang H, Zhang X: Confidence band for the difference between two direct adjusted survival curves. *Journal of Statistical Software* 2016;70:Snippet 2
21. Sorensen HT, Thulstrup AM, Mellekjaer L, Jepsen P, Christensen E, Olsen JH, Vilstrup H: Long-term survival and cause-specific mortality in patients with cirrhosis of the liver: a nationwide cohort study in Denmark. *J Clin Epidemiol* 2003;56:88-93
22. Roberts SE, Goldacre MJ, Yeates D: Trends in mortality after hospital admission for liver cirrhosis in an English population from 1968 to 1999. *Gut* 2005;54:1615-1621
23. Ratib S, Fleming KM, Crooks CJ, Walker AJ, West J: Causes of death in people with liver cirrhosis in England compared with the general population: a population-based cohort study. *Am J Gastroenterol* 2015;110:1149-1158
24. Lazo M, Hernaez R, Bonekamp S, Kamel IR, Brancati FL, Guallar E, Clark JM: Non-alcoholic fatty liver disease and mortality among US adults: prospective cohort study. *Bmj* 2011;343:d6891
25. Jepsen P, Gronbaek H: Prognosis and staging of non-alcoholic fatty liver disease. *Bmj* 2011;343:d7302
26. Sung KC, Ryu S, Lee JY, Kim JY, Wild SH, Byrne CD: Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver. *J Hepatol* 2016;65:791-797
27. Bell S, Daskalopoulou M, Rapsomaniki E, George J, Britton A, Bobak M, Casas JP, Dale CE, Denaxas S, Shah AD, Hemingway H: Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. *BMJ* 2017;356:j909
28. Sahlman P, Nissinen M, Pukkala E, Farkkila M: Cancer incidence among alcoholic liver disease patients in Finland: A retrospective registry study during years 1996-2013. *Int J Cancer* 2016;138:2616-2621
29. Sanna C, Rosso C, Marietti M, Bugianesi E: Non-Alcoholic Fatty Liver Disease and Extra-Hepatic Cancers. *International journal of molecular sciences* 2016;17
30. Hwang ST, Cho YK, Park JH, Kim HJ, Park DI, Sohn CI, Jeon WK, Kim BI, Won KH, Jin W: Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps. *J Gastroenterol Hepatol* 2010;25:562-567
31. Wong VW, Wong GL, Tsang SW, Fan T, Chu WC, Woo J, Chan AW, Choi PC, Chim AM, Lau JY, Chan FK, Sung JJ, Chan HL: High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. *Gut* 2011;60:829-836
32. Morling JR, Fallowfield JA, Guha IN, Williamson RM, Ali M, Glancy S, Strachan MW, Price JF: Clinically significant chronic liver disease in people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *QJM : monthly journal of the Association of Physicians* 2016;109:249-256

33. Vernon G, Baranova A, Younossi ZM: Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Alimentary Pharmacology & Therapeutics* 2011;34:274-285
34. Rotman Y, Sanyal AJ: Current and upcoming pharmacotherapy for non-alcoholic fatty liver disease. *Gut* 2017;66:180-190
35. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, Guo K, Abouda G, Aldersley MA, Stocken D, Gough SC, Tomlinson JW, Brown RM, Hubscher SG, Newsome PN: Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2015;

**Table 1**

International Classification of Disease (ICD) codes used to define disease groups of interest.

<b>Disease group</b>	<b>Individual disease name(s)</b>	<b>Diagnosis/procedure codes*</b>
Viral hepatitis	viral hepatitis	(D070.3), (D070.5), (D070.9); [B16, B17, B18]
Autoimmune hepatitis and primary biliary cirrhosis	autoimmune hepatitis and primary biliary cirrhosis:	(571.4), (571.6), [K75.4, K74.3]
Hemochromatosis	hemochromatosis	275.0) [E83.1]
Unspecified liver disease	cirrhosis hepatic fibrosis or sclerosis or fibrosis with sclerosis portal hypertension	571.5, K74.6 571.9, K74.0, K74.1, K74.2 572.3, K76.6
Alcoholic liver disease (ALD)	alcoholic liver disease	(571.0), (571.2), (571.3), [K70].
Non-alcoholic fatty liver disease (NAFLD)	other chronic non-alcoholic liver disease fatty (change of) liver, not elsewhere classified non-alcoholic steatohepatitis	571.8 K76. K75.8
Cardiovascular disease (CVD) mortality	coronary heart disease cerebrovascular disease heart failure sudden cardiac death	I20-I25 I60-I69, G45 I50 I46.1
Liver disease mortality	all liver disease except HCC, toxic liver disease and liver diseases classified elsewhere	K70, K72-76
Other mortality	all other causes of death	Any code not in the above four cells
Prevalent and incident CVD	acute coronary syndrome/ myocardial infarction stroke heart failure coronary revascularisation procedures and carotid revascularisation procedures	410, I20-I22 431-437, I61, I63, I64 428, I50 K40-K46, K49, K50.1, K50.8, K75 and L29.4, L29.5, L31.1, L34.4
Hepatocellular carcinoma (HCC)	hepatocellular carcinoma	C22.0
Other cancer mortality	all cancer except HCC	All C codes except C22.0

\*ICD-9 codes are numerical, ICD-10 codes are alpha-numerical, fourth revision of the Office for Population Censuses and Surveys procedure codes are given in italics. All deaths were coded using ICD-10 codes

**Table 2**

Descriptive characteristics of people diagnosed with type 2 diabetes in Scotland aged 40-89 years between 2004 and 2013 with record of one or more hospital admissions and complete data available, by liver disease status.

Variable	ALD (n = 1,707)	NAFLD (n = 1,452)	No liver disease (n = 131,209)
Age (years) at diagnosis with diabetes: mean (SD)	59.3 (9.8) p < 0.001*	58.7 (11.0) p < 0.001*	62.7 (12.0)
Male: n (% of total)	1,219 (71.4) p < 0.001†	685 (47.2) p < 0.001†	72,017 (54.9)
Deprivation: n (% of total) in SIMD quintile			
1 (most deprived)	593 (34.7)	348 (24.0)	30,745 (23.4)
2	405 (23.7)	367 (25.3)	30,111 (22.9)
3	276 (16.2)	275 (18.9)	26,769 (20.4)
4	250 (14.6)	260 (17.9)	24,270 (18.5)
5 (least deprived)	183 (10.7) p < 0.001‡	202 (13.9) p = 0.201‡	19,314 (14.7)
HbA1c, mmol/mol: mean (SD)§	60.6 (25.6) p < 0.001	63.7 (21.9) p = 0.008	63.1 (22.6)
BMI, kg / m <sup>2</sup> : mean (SD)§	29.5 (6.5) p < 0.001*	33.6 (6.6) p = 0.082#	32.1 (6.4)
Smoking: n (% of total)			29,409
current smoker	770 (45.1)	375 (25.8)	(22.4) 47,916
former smoker	489 (28.6)	500 (34.4)	(36.5) 53,884
never smoked	448 (26.2) p < 0.001‡	577 (39.7) p = 0.008‡	(41.1)
Systolic BP, mm Hg: mean (SD)§,**	135(19.5) p < 0.001*	137 (17.7) p = 0.002#	138 (17.9)
Hypertensive/on treatment: n (% of total)	1,568 (91.9) p < 0.001†	1,307 (90.0) p = 0.027†	115,623 (88.1)
Total cholesterol, mmol/l: mean (SD)§,i	5.0 (1.5) p < 0.001*	5.2 (1.5) p = 0.021*	5.1 (1.3)
High cholesterol/on treatment: n (% of total)	1,314 (77.0) p < 0.001†	1,309 (90.2) p = 0.073†	120,209 (91.5)
History of CVD before diabetes: n (% of total)	315 (18.4) p = 0.556†	276 (19.0) p = 1.000†	25,008 (19.1)
History of cancer before diabetes: n (% of total)	188 (11.0) p < 0.001†	259 (17.8) p = 0.033†	20,687 (15.8)

All hypothesis test results (p values) represent comparison of specific liver disease group (e.g. ALD) with the 'no liver disease' group (rightmost column of table).

\*Two-sample t-test (equality of variances rejected, so degrees of freedom derived via Satterthwaite's approximation [Satterthwaite, 1946]).

†Fisher's exact test.

‡Chi-square test.

§Value is that measured at closest point in time to date of diagnosis with diabetes.

||Mann-Whitney test.

¶Numbers of missing values are: 449 (ALD), 359 (NAFLD / NASH), 32,828 (no liver disease).

#Two-sample t-test (equality of variances assumption upheld).

\*\*Numbers of missing values are: 10 (ALD), 11 (NAFLD / NASH), 528 (no liver disease)



**Table 3**

Outcomes, duration of follow-up and crude event rates for people diagnosed with type 2 diabetes in Scotland aged 40-89 years between 2004 and 2013 with one or more hospital admission records and complete data available, by liver disease status.

	ALD (n = 1,707)			NAFLD (n = 1,452)			No liver disease (n = 131,209)		
outcome	event s	person -years (p-y)	event rates per 1,00 0 p-y	event s	person -years (p-y)	event rates per 1,00 0 p-y	events	person- years (p-y)	event rates per 1,00 0 p-y
incident/ recurren t CVD	378	6,746	56.0	320	6,219	51.5	21,87 3	567,204	38.6
incident/ recurren t HCC	64	7,262	8.8	19	7,054	2.7	114	618,794	0.2
incident/ recurren t cancer excl. HCC	204	7,003	29.1	157	6,720	23.4	14,98 7	586,336	25.6
all- cause mortality	724	7,346	98.6	221	7,092	31.2	16,20 3	618,871 2	26.2
CVD mortality	75		10.2	41		5.8	4428		7.2
HCC mortality	36		4.9	8		1.1	153		0.2
cancer mortality excl. HCC	72		9.8	38		5.4	5,474		8.8
other causes of death	179		24.4	80		11.3	6,133		9.9

**Table 4**

Associations between history of hospital admission with alcoholic liver disease (ALD) or non-alcoholic fatty liver disease (NAFLD) and incident/recurrent CVD, cancer and mortality among people with type 2 diabetes with one or more hospital admission records and no record of other chronic liver diseases aged 40-89 years in Scotland from 2004-2013.

Outcome	Hazard ratios (95% CI)	
	ALD (n = 1,707)	NAFLD (n=1,452)
Incident or recurrent CVD event*	1.59 (1.43, 1.76)	1.70 (1.52, 1.90)
Incident or recurrent HCC <sup>†</sup>	41.7 (30.0, 57.8)	19.3 (11.8, 31.4)
Incident or recurrent cancer excluding HCC <sup>‡</sup>	1.28 (1.12, 1.47)	1.10 (0.94, 1.29)
All-cause mortality <sup>§</sup>	4.85 (4.49, 5.23)	1.60 (1.40, 1.83)
CVD mortality*	2.05 (1.63, 2.58)	1.15 (0.85, 1.57)
HCC mortality <sup>†</sup>	20.5 (13.9, 30.1)	6.16 (3.02, 12.6)
Cancer mortality (excluding HCC) <sup>‡</sup>	1.24 (0.98, 1.57)	0.76 (0.55, 1.04)
Other causes of death	3.50 (3.00, 4.07)	1.60 (1.28, 1.99)

Hazard ratios are expressed relative to group with no record of any of the specified liver disease types (n = 131,209). See text for definitions.

\*Model includes prevalent CVD (i.e. CVD diagnosed prior to diabetes) as additional predictor.

<sup>†</sup>Model includes prevalent HCC as additional predictor.

<sup>‡</sup>Model includes prevalent non-HCC cancer as additional predictor.

<sup>§</sup>Model includes prevalent CVD and prevalent cancer (any site) as additional predictors.

TABLE 1: Results (hazard ratios with 95% confidence limits) from sensitivity analysis of incident outcomes (for comparison to estimates for incident/recurrent outcomes reported in table 4).

<b>INCIDENT CVD</b>	
(ALD: n = 1,392; NAFLD: n = 1,176; no liver disease: n = 106,201)	
ALD	NAFLD / NASH
1.75 (1.54, 1.99)	1.55 (1.33, 1.80)
<b>INCIDENT HCC</b>	
(ALD: n = 1,699; NAFLD: n = 1,451; no liver disease: n = 131,204)	
ALD	NAFLD / NASH
40.99 (29.40, 57.14)	18.46 (11.19, 30.47)
<b>INCIDENT CANCER EXCLUDING HCC</b>	
(ALD: n = 1,526; NAFLD: n = 1,193;no liver disease: n = 110,523)	
ALD	NAFLD / NASH
1.33 (1.13, 1.55)	1.11 (0.91, 1.35)

FIGURE 1: Selection of cohort of people with type 2 diabetes of 40-89 years of age diagnosed in Scotland 2004-2013 who had a record of at least one hospital admission, no record of any of viral hepatitis, auto-immune hepatitis, haemochromatosis or liver disease of unspecified cause and who had complete data for socio-economic status, smoking status, hypertension/treatment status, high cholesterol/treatment status and HbA1c.

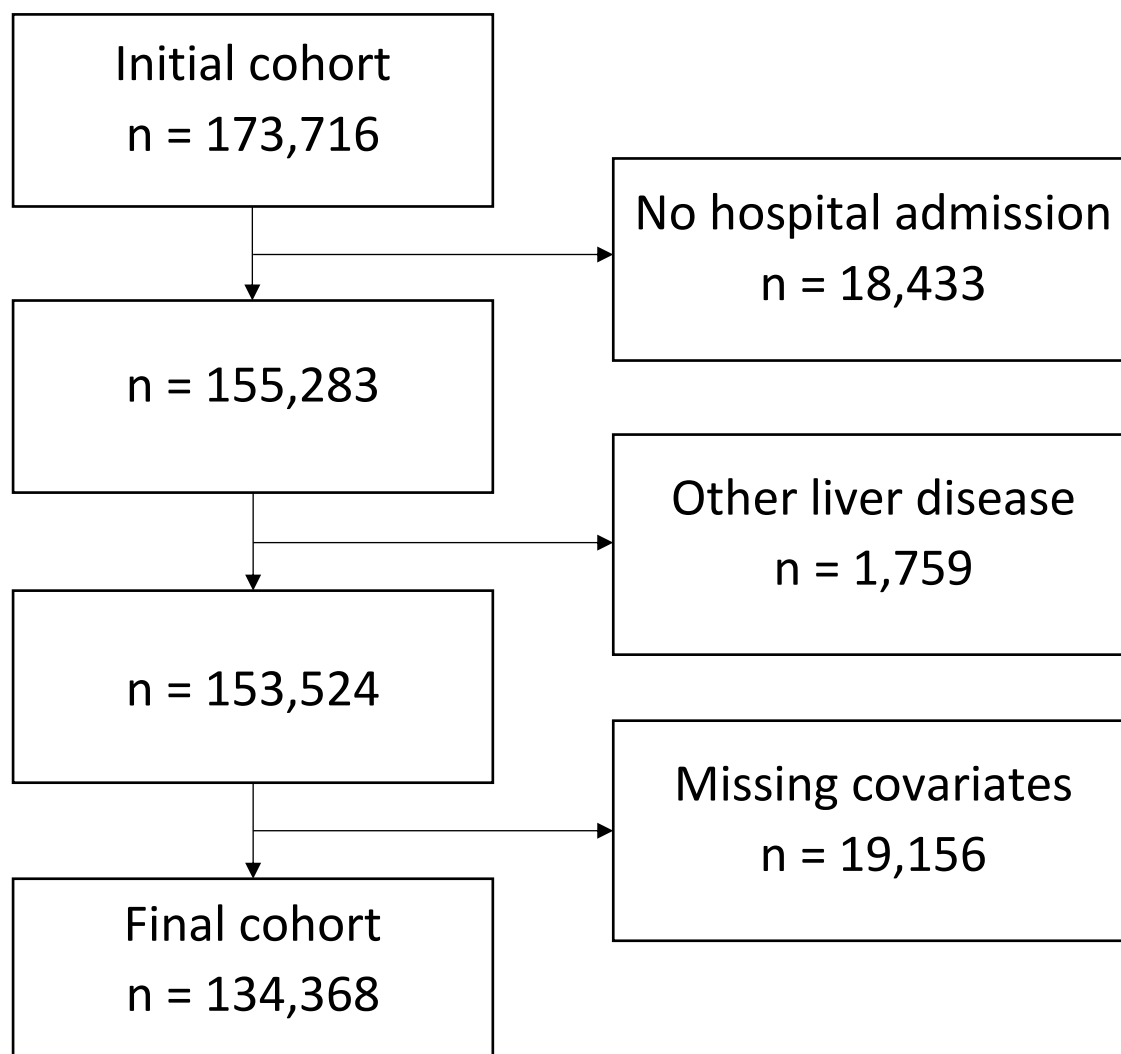
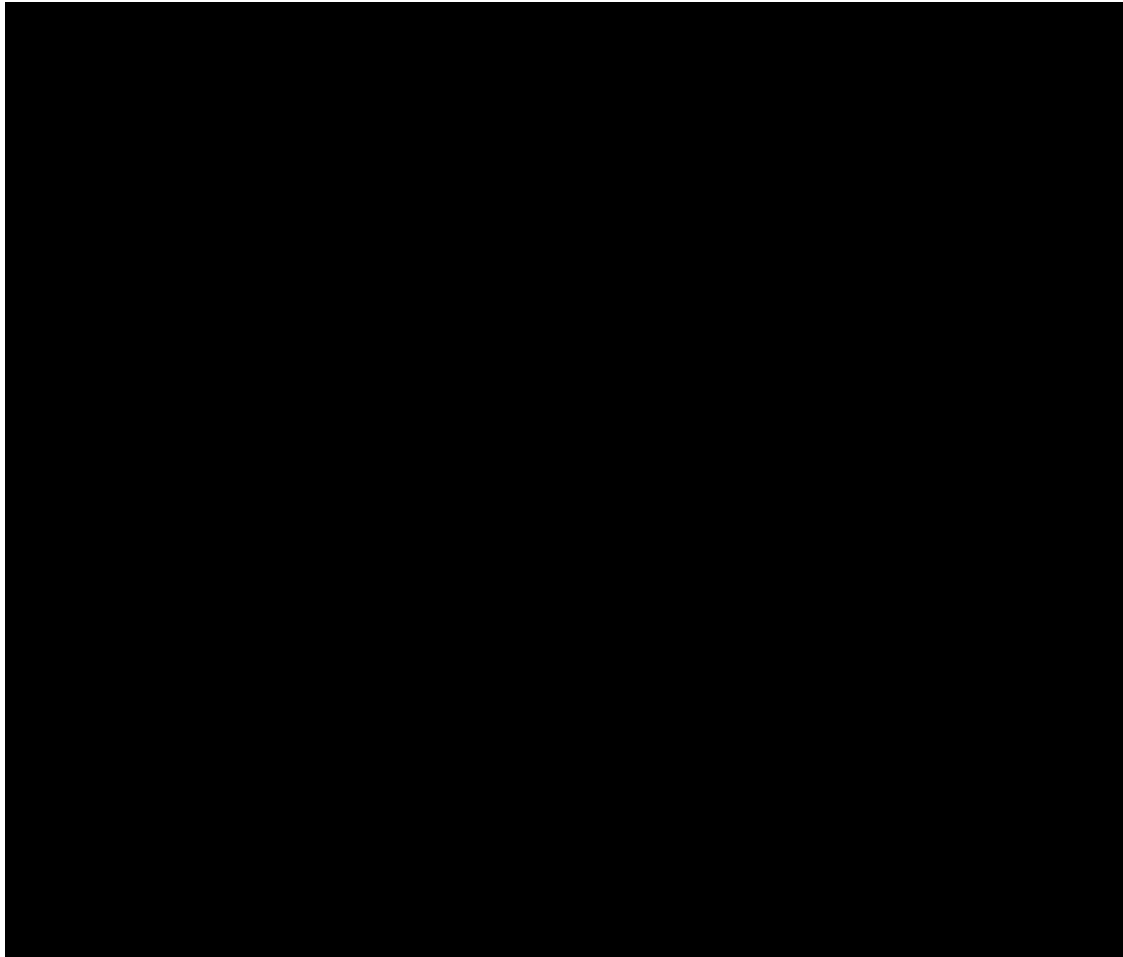
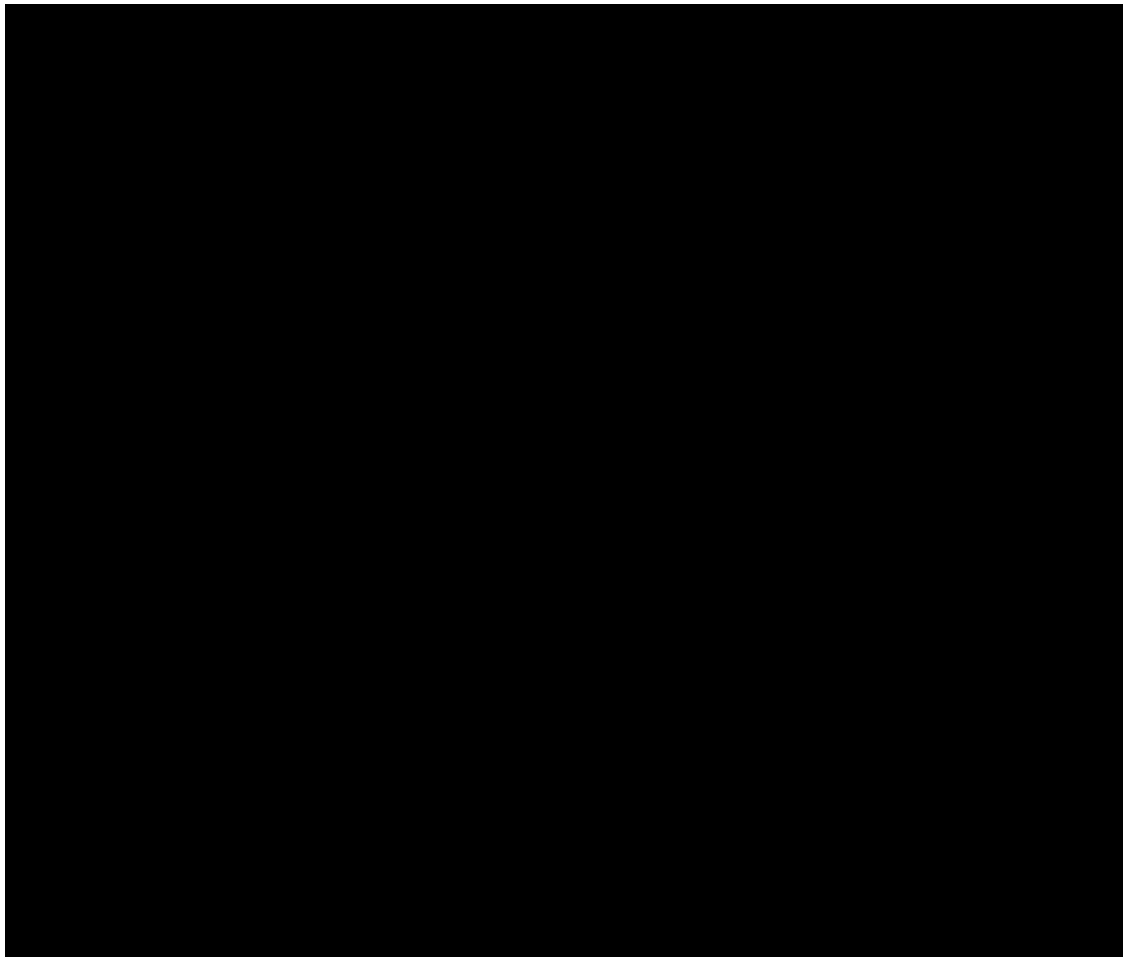


FIGURE 2: Difference in direct adjusted survival (outcome: all-cause mortality) between those with alcoholic liver disease (ALD) and those with no liver disease, with 95% confidence band. Cohort is people diagnosed with type 2 diabetes in Scotland aged 40-89 years between 2004 and 2013, restricted to those with complete data available. Values < 0 indicate reduced survival probability in group with ALD.



Time from diabetes diagnosis (years)

FIGURE 3: Difference in direct adjusted survival (outcome: all-cause mortality) between those with NAFLD and those with no liver disease, with 95% confidence band. Cohort is people diagnosed with type 2 diabetes in Scotland aged 40-89 years between 2004 and 2013, restricted to those with complete data available. Values < 0 indicate reduced survival probability in group with NAFLD.



Time from diabetes diagnosis (years)